Appendix: Supplementary material [posted as supplied by author]

Secondary outcomes

Distress and overall symptom burden

Distress was assessed in two RCTs.[28,34] Results were inconclusive (P=0.32) (table E).

Overall symptom burden (Edmonton Symptom Assessment System, ESAS) was assessed in two RCTs.[36,33] Results for cancer patients were inconclusive[33] whereas acute heart failure patients might benefit from SPC[36] (fig C). The quality of evidence of the pooled effect was low (downgraded due to serious risk of bias and inconsistency) (table D).

Depression

The Patient Health Questionnaire 9 (PHQ-9) for assessing depression was used in three studies.[37,36,38] In one RCT,[37] results did not differ between groups (P=0.82) and in another, [36] the clinical relevance of the effect was questionable. In the remaining RCT,[38] depression was considerably reduced on the PHQ-9 and the Hospital Anxiety and Depression Scale (HADS) (table E, fig D).

Anxiety

Anxiety was measured in three studies with three different assessment tools.[36,38,32] Effects were very small and contradictory (table E).

Dyspnoea

Dyspnoea was assessed in two RCTs but from one study,[32] no firm conclusions can be drawn due to baseline differences and lack of reporting of SDs and p-values (table E). No group differences were reported in the other RCT.[34]

Survival

Of six studies evaluating survival,[37,36,38,30,32,34] four RCTs could be included in a meta-analysis, but results were inconclusive. The sensitivity analysis early versus not early and a subgroup analysis by age are also provided (fig E).

Social well-being

The impact of SPC on social activities was assessed in one RCT.[34] The results slightly favoured SPC but the effect size was small (table E).

Place of death

Place of death was reported in four studies.[29,30,32,34] In the study of Jordhøy et al, SPC patients had a 67% higher probability to die at home (54 of 219 (25%) versus 26 of 176 (15%); 95% CI 1.09 to 2.55; P=0.02) (table D). On the contrary, Gade et al reported more deaths in hospital for the SPC group compared with the standard care group (47 (17.1%) versus 19 (8.0%); P=0.002).[30] The other two studies did not allow any judgment because of very low death rates.[29,32] Meta-analysis was not possible because the studies assessed different places of death.

Cost of care

Three studies (30%) collected data on resource utilization.[30,32,45] In a secondary analysis of a previous RCT,[38] Greer et al concluded that neither the average mean costs per day nor expenses for hospice care differ between SPC and standard care. However, in the same study, expenses for chemotherapy were significantly reduced by $-757 (P=0.03) for SPC versus standard care. In the trial of Gade et al, the mean health costs per patient were significantly lower for SPC versus standard care (SPC-standard care: -$7,483, P=0.001) while hospitalization costs did not differ (table F). In the study of Rabow et al, no differences were reported in the mean charge per patient for all medical centre services.

Nausea

Nausea was assessed in two studies[36,34] but no effect could be observed (table E).

Spiritual well-being

The results of Cheung et al[29] favoured SPC but no information concerning SDs or p-values was given (table E).

Satisfaction with care

Satisfaction with care was assessed in five RCTs by different measures which prohibited meta-analysis.[33,29,30,32,31] The results were contradictory (table E).

Fatigue

Jordhøy et al[34] reported fatigue but no noteworthy differences were observed (table E).

table A: MEDLINE Ovid search strategy (July 2016)

 # search

1. *Palliative Care/
2. palliative care.ab,ti.
3. support* care.ab,ti.
4. early palliative care.af.
5. special* palliative care.af.
6. terminal care.ab,ti.
7. coordinat* care.ab,ti.
8. comprehensiv* care.ab,ti.
9. hospice care.ab,ti.
10. Palliative Medicine/
11. Palliative Medicine.ab,ti.
12. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13. intervention.ab,ti.
14. team.ab,ti.
15. service.ab,ti.
16. visit.ab,ti.
17. consult*.ab,ti.
18. 13 or 14 or 15 or 16 or 17
19. randomized controlled trial.pt.
20. controlled clinical trial.pt.
21. randomized.ab.
22. placebo.ab.
23. clinical trials as topic.sh.
24. randomly.ab.
25. trial.ti.
26. 19 or 20 or 21 or 22 or 23 or 24 or 25
27. ((comment or editorial or meta-analysis or practice-guideline or review or letter or journal correspondence) not "randomized controlled trial").pt.
28. (random sampl$ or random digit$ or random effect$ or random survey or random regression).ti,ab. not "randomized controlled trial".pt.
29. exp animals/ not humans.sh.
30. child*.mp. or Child/
31. 27 or 28 or 29 or 30
32. 12 and 18 and 26
33. 32 not 31

Table B: Excluded studies after reading full text

Reference	Reason for exclusion
Addington-Hall et al, 1992	Intervention not appropriate: not a multiprofessional team
Ahronheim et al, 2000	Outcomes not appropriate
Aiken et al, 2006	Intervention not appropriate: home-based case management
Bakitas et al, 2009	Intervention not appropriate: not a multiprofessional team
Bakitas et al, 2014	Intervention not appropriate: not a multiprofessional team
Bakitas et al, 2015	Intervention not appropriate: not a multiprofessional team
Bekelman et al, 2015	Intervention not appropriate: team reviewed the electronic health records
Casarett et al, 2005	Intervention not appropriate: intervention was designed to help physicians to identify patients
Chochinov et al, 2011	Intervention not appropriate: not a multiprofessional team
Costantini et al, 2011	Study design not appropriate: protocol
Costantini et al, 2014	Study design not appropriate: uncontrolled before–after intervention cluster trial
Edmonds et al, 2010	Setting: patients were treated at home (87%)
Engelhardt et al, 2006	Intervention not appropriate: coordination (not treatment), information and empowerment
Farquhar et al, 2009	Study aim not appropriate: focusses on breathlessness
Farquhar et al, 2014	Study aim not appropriate: focusses on breathlessness
Greer et al, 2011	Outcomes not appropriate
Grudzen et al, 2013	Multiple publication: full text was identified; see Grudzen et al (2016); NCT01358110
Grudzen et al, 2015	Multiple publication: full text was identified; see Grudzen et al (2016); NCT01358110
Hannon et al, 2014	Participants not appropriate: bereaved caregivers
Higginson et al, 2008	Outcomes not appropriate; results published by Edmonds et al (2010)
Higginson et al, 2008a	Multiple publication: NCT00364936; see Higginson et al (2009)
Higginson et al, 2009	Setting: patients were treated at home (87%)
Higginson et al, 2014	Study aim not appropriate: focusses on breathlessness
Hopp et al, 2016	Outcomes not appropriate
Jones et al, 2013	Participants not appropriate: cancer survivors
Kistler et al, 2015	Multiple publication: NCT01358110; see Grudzen et al (2016)
Lo et al, 2009	Study aim not appropriate: psychometric properties of a measure of satisfaction

Lowery et al, 2013	Intervention not appropriate: not a multiprofessional team
McCorkle et al, 1998	Intervention not appropriate: not a multiprofessional team
McMillan et al, 2007	Participants not appropriate: caregivers
Meyers et al, 2011	Intervention not appropriate: cognitive-behavioral problem-solving educational intervention
Moore et al, 2002	Intervention not appropriate: not a multiprofessional team
Pantilat et al, 2010	Intervention not appropriate: not a multiprofessional team
Pirl et al, 2012	Study design not appropriate: secondary analysis
Raftery et al, 1996	Intervention not appropriate: not a multiprofessional team
Schofield et al, 2009	Multiple publication: presentation; see Schofield et al (2013)
Schofield et al, 2013	Intervention not appropriate: needs assessment, not a multiprofessional team
Sun et al, 2014	Study design not appropriate: Not an RCT
Tattersall et al, 2011	Intervention not appropriate: not a multiprofessional team
Vanbutsele et al, 2014	Outcomes not appropriate: preliminary data
Veronese et al, 2015	Setting: The vast majority of patients were treated at home (personal communication)
Wentlandt et al, 2012	Study aim not appropriate: associations of clinician-patient communication
Zimmermann et al, 2012	Multiple publication: NCT01248624; see Zimmermann et al (2014)

Table C: Additional patients' characteristics

Reference	Patients within groups	Age within groups, mean (SD)	Females	Females within groups	ITT, Comments
Grudzen et al, 2016[37]	IG: 69 (51%) CG: 67 (49%)	IG: 55.1 (13.1) CG: 57.8 (14.7)	76 (56%)	IG: 39 (57%) CG: 37 (55%)	-ITT: yes; baseline-values-carried-forward
Sidebottom et al, 2015[36]	IG: 116 (50%) CG: 116 (50%)	IG: 76.0 (11.9) CG: 70.9 (13.6)	110 (47%)	IG: 61 (52.6%) CG: 49 (42.2%)	-ITT: yes -unprecise: three primary outcomes assessed in three points of time
Zimmermann et al, 2014[33]	IG: 228 (50%) CG: 233 (50%)	IG: 61.2 (12.0) CG: 60.2 (11.3)	261 (57%)	IG: 136 (59.6%) CG: 125 (53.6%)	-ITT: yes -primary outcome assessed after 3 months
Wallen et al, 2012[28]	IG: 76 (50%) CG: 76 (50%)	IG: 52.4 (10.4) CG: 52.4 (3.0)	71 (47%)	IG: 32 (42.1%) CG: 39 (51.3%)	-ITT: yes -follow-up staging visits at 4–6 weeks, 3, 6, 9, and 12 months -CG: crossover to IG allowed

Cheung et al, 2010[29]	IG: 10 (50%) CG: 10 (50%)	IG: 83* CG: 72*	12 (60%)	IG: 5 (50%) CG: 7 (70%)	-ITT: yes but not for questionnaire data -intervention not described
Temel et al, 2010[38]; Greer et al 2014[45]	IG: 77 (51%) CG: 74 (49%)	IG: 65.0 (9.7) CG: 64.9 (9.4)	78 (52%)	IG: 42 (55%) CG: 36 (49%)	-ITT: yes; baseline-observation-carried-forward stated but not applied
Gade et al, 2008[30]	IG: 280 (54%) CG: 237 (46%)	IG: 73.6 (12.6) CG: 73.1 (13.2)	283 (55%)	IG: 162 (59%) CG: 121 (51%)	-ITT: n.a. -patient and proxy data combined
Rabow et al, 2004[32]	IG: 50 (56%) CG: 40 (44%)	IG: 67.9 (13.9) CG: 69.4 (11.2)	58 (64%)	IG: 37 (74%) CG: 21 (52%)	-ITT: n.a. -patients with COPD, CHF, or cancer diagnoses
Hanks et al, 2002[31]	IG: 175 (67%) CG: 86 (33%)	IG: 68.5 (26-93)§ CG: 68.5 (34-91)§	119 (46%)	IG: 72 (41%) CG: 47 (55%)	-ITT: yes -2:1 randomization (IG:CG)
Jordhøy et al, 2001[34],2000[35]	IG: 235 (54%) CG: 199 (46%)	IG: 70* CG: 69*	204 (47%)	IG: 103 (44%) CG: 101 (51%)	-ITT: n.a. -health-care districts defined as clusters; at home: (<24%) -last value carried forward
Total	IG: 1316 (54%) CG: 1138 (46%)	Range: 55.1-83*	1272 (52%)	IG: 689 (54%) CG: 583 (46%)	Total number of randomised patients: 2454

* median, § range

CG: control group; **ED**: emergency department; **ICU**: intensive care unit; **IG**: intervention group; **n.a.**: not available; **SPC**: specialist palliative care; **StC**: standard care

Table D: Summary of findings and quality of evidence (GRADE)

Specialist palliative care compared to standard care (StC) for patients with advanced disease

Patient or population: patients with advanced disease
Setting: hospital

Intervention: specialist palliative care

Comparison: StC

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of evidence (GRADE)	Comments
	Risk with StC	Risk with SPC				
ESAS Scale: 0-90 follow up: mean 3 months	Mean changes from baseline: -4·7 and +2·1	Mean 3·63 points lower (5·88 lower to 1·38 lower) than in StC	-	467 (2 RCTs)	⨁⨁◯◯ LOW [1,2]	-low values mean improvement -weighed mean baseline values: 26 points (Sidebottom: 31·9; Zimmermann: 23·0) -fig C
Depression follow up: mean 3 months	-	SMD 0·51 SD lower (1·03 lower to 0·01 higher) than in StC	-	454 (3 RCTs)	⨁◯◯◯ VERY LOW [1,2,3]	-lower values mean improvement -effect: 0·2-0·5=small, 0·5, 0·8=moderate, >0·8=large effect -fig D4
Survival	-	HR 0·97 (0·63 higher to 1·48 higher)	-	953 (4 RCTs)	⨁◯◯◯ VERY LOW [4,5]	-HR<1 favors SPC (StC as reference) -fig E
Place of death: home vs not follow up: mean 2 years	149 per 1000	**250 per 1000** (163 to 381)	**RR 1·67** (1·09 to 2·55)	395 (1 RCT)	⨁⨁◯◯ LOW [6,7]	-RR>1 indicate that more SPC patients died at home -not home: nursing home / hospital -results from Jordhøy et al (2000)

CI: Confidence interval; **ESAS:** Edmonton Symptom Assessment System; **GRADE**: Grades of Recommendation, Assessment, Development and Evaluation; **QoE:** Quality of Evidence; **RR:** Risk ratio; **SD:** standard deviation; **SMD:** Standardized mean difference; **SPC:** specialist palliative care

***The risk in SPC** (and its 95% CI) is based on the assumed risk in StC and the **relative effect** of the intervention (and its 95% CI).

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Footnotes

1. QoE downgraded by one level because of serious risk of bias: Blinding of participants and personnel is hardly possible in SPC studies; assessment of a subjective outcome
2. QoE downgraded by one level because of serious inconsistency: I2 >50%.
3. QoE downgraded by one level because of serious imprecision: Wide range of 95% CI; includes large & very small effects & crosses 0 (P=0·05).
4. QoE downgraded by two levels because of very serious inconsistency: Study effects in both directions lead to very high inconsistency (I2=77%).
5. QoE downgraded by two levels because of very serious imprecision: The 95% CI has a wide range and includes effects in both directions.
6. QoE downgraded by one level because of serious risk of bias: Blinding of participants and personnel is hardly possible in SPC studies; even decisions concerning place of death may not be free of bias.
7. QoE downgraded by one level because of serious imprecision: The 95% CI has a wide range and includes large and very small effects.

Table E: Summary of outcomes: QoL and symptoms

RCT	Outcome measure [mean (SD) or (95% CI)] and observed effect[#]		Comments*
Grudzen 2016[37]	**FACT-G, mean change (0-108)↑** IG: 5·91 (SD 16·65), CG: 1·08 (SD 16·00); P=0·03, **effect +**		-results at week 12 -QoL baseline difference (CG: 9·82, IG: 53·56); MDD (yes/no); yes= PHQ>5
	PHQ-9 [% with MDD] (0-27)↓ IG: 20/69 (29%)*, CG: 21/67 (30·8%)*; P=0·82, **effect 0/+**		
Sidebottom 2015[36]	**MLHF, mean difference between groups (0-105) ↓** CG-IG (95% CI): -3·06 (-2·75 to -3·37); P<0·001, **effect +**		-results at month 3 -effects at month 1 smaller -adjusted for age, gender and marital status
	ESAS (0-10)↓ IG-CG (95% CI): **Pain**: -0·44 (-0·13 to -0·75); P=0·005, **effect: +** **Tiredness**: -0·86 (-0·55 to -1·17); P<0·001, **effect: +** **Nausea**: 0·18 (-0·13 to 0·49); P=0·260, **effect: 0/-** **Drowsiness**: -0·12 (-0·43 to 0·19); P=0·442, **effect: 0/+** **Appetite**: -0·44 (-0·75 to -0·13); P=0·005, **effect: +** **Short of breath**: -1·08 (-0·77 to -1·39); P<0·001, **effect: +** **Total Score (0-90)↓:** -4·31 (-4·62 to -4·00); P<0·001, **effect: +**	**PHQ-9, (0-27)↓** IG-CG (95% CI): -0·72 (-1·03 to -0·41), P<0·001, **effect: +** **ESAS (0-10)↓** IG-CG (95% CI): **Depression**: -1·01 (-1·32 to -0·70); P<0·001, **effect: +** **Anxiety**: -0·38 (-0·07 to -0·69); P=0·017, **effect: +** **Well-being**: -0·15 (-0·46 to 0·15); P=0·333, **effect: +**	
Zimmermann 2014[33]	**change for FACIT-Sp (0–156)↑** IG: 1·60 (SD 14·46), CG: –2·00 (SD 13·56) IG-CG (95% CI): 3·56 (–0·27 to 7·40); P=0·07; d=0·26, **effect 0/+**	**change for QUAL-E (21–105)↑** IG: 2·33 (SD 8·27), CG: 0·06 (SD 8·29) IG-CG (95% CI): 2·25 (0·01 to 4·49); P=0·05; d=0·28, **effect 0/+**	-results at month 3 -ICC≤0·036, except for ESAS: ICC=0·067 -effects of month 4 greater than month 3 -robust results in sensitivity analyses -adjusted for cluster and baseline covariates
	Change for ESAS (0-90)↓ IG: 0·14 (SD 16·93), CG: 2·12 (SD 13·88) IG-CG: –1·70 (95% CI -5·26 to 1·87), P=0·33; d=-0·13, **effect: 0/+**	**Change for FAMCARE-P16 (16–80)↑** IG: 2·33 (SD 9·10), CG: –1·75 (SD 8·21) IG-CG: 3·79 (95% CI 1·74 to 5·85), P<=0·001; d=0·47, **effect: +**	
Wallen 2012[28]	QoL not assessed		-results at month 3 -3 primary outcomes but time of measurement not specified -results adjusted for baseline & CES-D
	GPS pain intensity (0-20)↓ IG-CG: -1·54; P=0·1356, **effect 0/+** **GPS unpleasantness (0-20)↓** IG-CG: -0·59; P=0·55, **effect 0/+**	**symptom distress (1-5)↓** IG-CG: 1·58; P=0·32, **effect 0/-** **CES-D (depression) (0-60)↓** n.a.	
Cheung 2010[29]	QoL not assessed		-multiple primary outcomes -results after discharge from intensive care unit or death (ie, family satisfaction) -patients' satisfaction not assessed -methodological limitations
	symptom management and comfort care (4–36)↑ IG: -1·0 (-3%), CG: -2 (-6%); P=0·91, **effect 0/+** **spiritual support, change (1–9)↑** IG: 0 (0%), CG: 1 (17%); P=0·41, **effect 0/+**	**quality of care by patients' families, change (20-180)↑** IG: -9·0 (-6%), CG: -9·5 (-6%); P=0·91, **effect 0/+**	
Temel 2010[38] **& Greer 2014**[45]	**TOI=FACT-L+LCS (0-84)↑** IG: 59·0 (SD 11·6), CG: 53·0 (SD 11·5) IG-CG: 6·0 (95% CI 1·5 to 10·4); P=0·009, d=0·52 **effect +**	**FACT-L (0-136)↑** IG: 98·0 (SD 15·1), CG: 91·5 (SD 15·8) IG-CG: 6·5 (95% CI 0·5 to 12·4); P=0·03, d=0·42 **effect +**	-results at week 12; adjustment for baseline -dichotomization: a) HADS-D/A: >7 (8-10: borderline, 11-21 abnormal b) PHQ-9: ≥5 including either anhedonia or depressed mood
	LCS (0-28)↑ IG: 21·0 (SD 3·9), CG: 19·3 (SD 4·2) IG-CG: 1·7 (95% CI 0·1 to 3·2); P=0·04, d=0·41, **effect 0/+** **PHQ-9 (0-27)↓** IG: 2/57 (4%), CG: 8/47 (17%); P=0·04, **effect +**	**HADS-D (0-21)↓** IG: 9/57 (16%), CG: 18/47 (38%); P=0·01, **effect + HADS-A (0-21)↓** IG: 14/57 (25%), CG: 14/47 (30%); P=0·66, **effect 0/+**	
Gade 2008[30]	**MCOHPQ (quality of life) (0-10)↑** IG: 6·4 (SD 2·3), CG: 6·3 (SD 2·1); P= 0·78, **effect 0/+**		-assessed 2 weeks after discharge, median days of stay: 7 -5 primary outcomes -no adjustment
	MCOHPQ (symptom control) (0-10)↓ IG: 4·0 (SD 1·7), CG: 4·1 (SD 1·8), P=0·91, **effect: 0/+** **MCOHPQ (satisfaction: place of care) (0-10)↑** IG: 6·8 (SD 1·0), CG: 6·4 (SD 1·1), P<0·001, **effect: +**	**MCOHPQ (0-10) (satisfaction: communication)↑** IG: 8·0 (SD 1·4), CG: 7·4 (SD 1·7), P<0·001, **effect: +** **MCOHPQ (emotional burden) (0-10)↓** IG: 7·0 (SD 1·4), CG: 6·7 (SD 1·5), P=0·07, **effect: 0/-**	
Rabow 2004[32]	**MQOLS-CA (0-100)↑** IG: 69·7, CG: 65·4; **effect n.a./+**		-results at 6 months -primary outcome and time not stated -no p-values at month 6, no SDs -baseline differences for dyspnea
	SOBQ Degree dyspnea interferes (0-105)↓ IG: 32·6, CG: 40·3, **effect: n.a./+** **SOBQ Frequency dyspnea limits activities (0-18) ↓**	**BPI: average pain (0-10)↓** IG: 4·8, CG: 4·9, **effect: n.a./+** **worst pain (0-10)↓** IG: 5·9, CG: 5·5, **effect: n.a./-** **least pain (0-10)↓** IG: 2·7, CG: 3·9,	

	IG: 5·8, CG: 6·5, **effect: n.a./+** **SWBS (spirituality) (20-120)↑** IG: 98·0, CG: 91·2, **effect: n.a./+** **GHAA (satisfaction) (20-120)↑** IG: 69·6, CG: 74·5, **effect: n.a./-**	**effect: n.a./+** **POMS (anxiety) (0-24)↓** IG: 6·6, CG: 5·5, **effect: n.a./-** **CES-D (depression) (0-60)↓** IG: 16·5, CG: 17·5, **effect: n.a./+**	-CES-D: ≥16 considered as depressed -adjusted for baseline scores
Hanks 2002[31]	**EORTC QLQ-C30 (0-100)↑** IG: 37·1->47·3, P<0·001; CG: 39·3->45·5, P<0·044; IG-CG: 2·35 (95% CI -3·7 to 8·4); P=0·45, **effect 0/+**		-results at week 1 -4 primary outcomes -19/86 (22%) switched to IG, 10 in week 1 -no p-values provided for MASQ -adjusted for baseline scores
	VAS most bothersome symptom (0-100)↑ IG: 28·7->48·5; P<0·001; CG: 35·1->49·3; P<0·001 IG-CG: 2·94 (95% CI -5·3 to 11·1); P=0·48, **effect: 0/+** **MPAC (mood) (0-100)↑** IG: 52·1->62·2; P<0·001 CG: 51·3->59·2; P=0·13 IG-CG: 3·97 (95% CI -2·5 to 10·4); P=0·23, **effect: 0/+** **WONCA scale (emotion) (0-5)↓** IG: 3·2->2·6; P<0·001 CG: 3·0->1·2; P=0·008 IG-CG: 0·105 (95% CI -0·27, 0·48); P=0·58, **effect: 0/+**	**MASQ (satisfaction) (1-4)↓** **Information given about illness** IG: 3·5 (SD 0·82), CG: 3·3 (SD 0·95), **effect: 0/-** **Information: treatment and medication** IG: 3·6 (SD 0·79), CG: 3·5 (SD 0·79), **effect: 0/-** **Availability of doctors for discussions** IG: 3·6 (SD 0·65), CG: 3·5 (SD 0·79), **effect: 0/-** **Availability of nurses for discussions** IG: 3·6 (SD 0·68), CG: 3·6 (SD 0·70), **effect: 0**	
Jordhøy 2001[34], **2000**[35]	**EORTC QLQ-C30 (global health) (0-100)↑** IG: 50 (SD 25·61), CG: 53 (SD 21·95) **effect n.a./-**		-results after 4 months -4 primary outcomes -significance level set at P=0·01 -all results: n.s. -no SDs or p-values reported but authors were contacted for SD values -no adjustment
	EORTC QLQ-C30: symptom scale (0-100)↓ **pain**: IG: 41 (SD 33·90), CG: 37 (SD 31·49), **effect: 0/-** **fatigue**: IG: 54 (SD 31·12), CG: 53 (SD 26·00), **effect: 0/-** **nausea/vomit:** IG: 14 (SD 21·73), CG: 14 (SD 19·07), **effect: 0** **dyspnea**: IG: 38 (SD 37·50), CG: 37 (SD 34·18), **effect: 0/-** **diarrhea**: IG: 19 (SD 28·17), CG: 21 (SD 28·46), **effect: 0/+** **constipation**: IG: 34 (SD 36·56), CG: 30 (32·92), **effect: 0/-**	**EORTC QLQ-C30: functioning (0-100)↑** **physical**: IG: 49 (SD 33·43), CG: 54 (SD 31·97), **effect: 0/-** **emotional**: IG: 71 (SD 23·00), CG: 75 (SD 23·23), **effect: 0/-** **social**: IG: 61 (SD 32·30), CG: 58 (SD 29·15), **effect: 0/+** **IES (psychologic distress)** **avoidance (0-38) ↓** IG: 13, CG: 13, **effect: 0** **intrusion (0-35) ↓** IG: 9, CG: 9, **effect: 0**	

Interpretation: ↑ **increasing score** means improvement for this outcome; ↓ **decreasing score** means improvement for this outcome; primary outcome of review (QoL): shaded, primary outcome of the RCTs: underlined

 # Definition of effects: **+**: statistically significant in favor of SPC; **0/+**: tendency in favor of SPC but not statistically significant; **n.a./+**: tendency in favor of SPC but no p-value provided; **0/-**: tendency in favor of CG but not statistically significant; **n.a./-**: tendency in favor of StC but no p-value provided; **-**: statistically significant effect in favor of CG

*****Outcomes analyzed at the point in time of measurement of the primary outcome as defined in the RCTs

Abbreviations: CG: control group; **CI**: confidence interval; **d**: Cohen's d (effect size: 0·2=small, 0·5=moderate, 0·8=large); **IG**: intervention group; **ICC**: intracluster correlation coefficient; **MDD:** major depressive disorder; **n.a.:** not available; **n.s.:** not (statistically) significant; **QoL**: quality of life; **RCT**: randomized controlled trial; **SD**: standard deviation

Tools: BPI: Brief Pain Inventory; **CES-D**: Center for Epidemiologic Studies Depression Scale; **EORTC QLQ-C30**: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; **ESAS**: Edmonton Symptom Assessment System; **FACIT-Sp**: Functional Assessment of Chronic Illness Therapy (FACIT)-spiritual Well-Being; **FACT-G**: Functional Assessment of Cancer Therapy (FACT) - General; **FACT-L**: FACT - Lung; **FAMCARE-P16**: patient satisfaction with care measure; **GHAA** Group Health Association of America Consumer Satisfaction Survey; **GPS**: Gracely Pain Scales; 13 verbal descriptors, each assessed with a visual analog scale (VAS); **HADS**, Hospital Anxiety and Depression Scale; (D: depression, A: anxiety); **IES**: Impact of Event scale; **LCS**: lung-cancer subscale of the FACT-L; **MASQ**: MacAdam's Assessment of Suffering Questionnaire; **MCOHPQ**: Modified City of Hope Patient Questionnaires; **MLHF**: Minnesota Living with Heart Failure; **MPAC**: Memorial Pain Assessment Card; **MQOLS-CA**: Multidimensional QoL Scale-Cancer Version; **PHQ-9**: Patient Health Questionnaire 9; **POMS**: Profile of Mood States; **QUAL-E**: QoL at End of Life; **SDS**: Symptoms Distress Scale; 11 symptoms; **SOBQ**: San Diego Shortness of Breath Questionnaire; **SWBS**: Spiritual Well-Being Scale; **TOI**: Trial outcome index (sum of LCS and physical and functional well-being of FACT-L); **WONCA** scale: World Organization of Family Doctors scale (emotional problems)

Table F: Summary of outcomes: survival, costs*, completion rate (CR)**

RCT	Secondary outcomes [effect#]			Comments
Grudzen 2016[37]	**median survival [days]↑** IG: 289 (95% CI 128 to 453) CG: 132 (95% CI 80 to 302); P=0·20; **effect: 0/+**		**CR:** IG: 40/69 (67%) CG: 33/67 (54%)	-survival measured at year 1; CR day 100
Sidebottom 2015[36]	**death within 6 months↓:** HR: 1·90 (95% CI 0·88 to 4·09); (CG=reference); P=0·101; **effect: 0/-**		**CR:** IG: 79/116 (68%); CG: 88/116 (76%)	-IG patients on average 5·1 years older than CG
Zimmer-mann 2014[23]	-		**CR:** IG: 140/228 (61%) CG: 141/233 (61%)	-CR at month 3; 4th month: attrition IG>CG
Wallen, 2012[28]	-		**CR:** IG: 54/76 (71%) CG: 53/76 (70%)	-CR at month 3
Cheung 2010[29]	-		**CR**: IG: 5/10 (50%) CG: 4/10 (40%)	-data collection at death or discharge
Greer 2014[§,45], based on Temel 2010[38]	**median survival [months]↑** IG: 11·6 (95% CI 6·4 to 16·9) CG: 8·9 (95% CI 6·3 to 11·4); P=0·02; **effect: +** **death within 37 months↓** HR: 0·59 (95% CI 0·39 to 0·88); (CG set as reference); P=0·01; **effect: +**	**average costs / day↓** IG-CG: -$117 (SD 436$); P=0·13; **effect: 0/+** **final 30 days of life, hospice care↓** IG-CG: $1,053 (SD $3,162); P=0·07; **effect: 0/-**	**final 30 days of life, expenses for chemotherapy↓** IG-CG: -$757 (SD $2,143); P=0·03; **effect: +** **CR:** IG: 60/77 (78%) CG: 47/74 (64%)	-deaths at week 12: IG: 10, CG: 17 -cost analysis :IG: 68, CG: 70 -only costs differences between groups published -survival measured at ca. 37 months
Gade 2008[30]	**median survival [days]↑** IG: 30 (IQR 6·1) CG: 36 (IQR 13·1) P=0·08; **effect: 0/-** **<u>total hospitalization costs</u>↓** IG: $22,987 (SD $40,088) CG: $17,521 (SD $18,959) IG-CG: $5466; P=0·08; **effect: 0/-**	**<u>Total mean health costs per patient</u>↓** IG $16,022 (SD 17,361) CG $23,505 (SD 25,197) IG-CG: -$7,483, P=0·001; **effect: +** **net savings per patient after subtracting the cost of staffing the IG↑** $4,855; **effect: n.a./+**	**CR** for QoL: IG: 199/280 (71%) CG: 191/237 (81%)	-CR at discharge -survival and costs for all health services within the 6 months following discharge -cost savings: no difference in number of readmissions but in ICU stays on readmission (IG: 12, CG: 21; P=0·04)
Rabow, 2004[32]	**Deaths within 12 months↓** IG: 10/50 (20%), CG: 5/40 (12·5%); **effect: n.a./-** **ED costs↓:** IG: $951 (SD $1,138) CG: $1,655 (SD $3,281) IG-CG: -$704 P=0·32; **effect: 0/+** **Costs: clinic visits↓** IG: $9,216 (SD $10,880) CG: $10,171 (SD $9,055) IG-CG: -$955 P=0·73; **effect: 0/+**	**Mean cost for all medical center services per patient↓** IG: $59,515 (SD $73,009), CG: $54,633 (SD $69,647), IG-CG: $4882 P=0·8; **effect: 0/-** **Urgent care costs↓** IG: $944 (SD $2,210) CG: $1,692 (SD $2,909) IG-CG: $-748 P=0·29; **effect: 0/+**	**Inpatient costs↓** IG: $39,450 (SD $54,285) CG: $39,363 (SD $66,611) IG-CG: $87 P=0·10; **effect: 0/-** **CR:** IG: 35/50 (70%) CG: 31/40 (78%)	-CR at month 12 -all analyses with IG 50 and CG 40 contradict dropout-rate -no imputation method stated -we stated CR numbers in our meta-analyses
Hanks 2002[31]	-		**CR**: IG: 117/175 (67%) CG: 56/86 (65%)	-CR at week 1 for QoL
Jordhøy, 2001[34], 2000[35]	**median survival [days]↑** IG: 99 (95% CI 79 to 119), CG: 127 (95% CI 88 to 166), P=0·1; **effect: 0/-** **death within 36·7 months ↓** HR: 1·20 (95% CI 0·96 to 1·50), P=0·1; **effect: 0/-**		**CR**: IG: 69/235 (29%) CG: 62/199 (31%)	-CR month 4 -median survival within 2 years -HR based on personal communication

Primary outcomes as stated by the authors are <u>underlined;</u> *absolute costs were inflation-adjusted for 2016 (http://www.usinflationcalculator.com/)

**Completion rate: for primary outcome or when main analyses were done; § only incremental costs provided

Definition of effects: **+**: statistically significant in favor of SPC; **0/+**: tendency in favor of SPC but not statistically significant; **n.a./+**: tendency in favor of SPC but no p-value provided; **0/-**: tendency in favor of CG but not statistically significant; **-**: statistically significant effect in favor of CG

CG: control group; **CI**: confidence interval; **HR**: hazard ratio; **ICU**: intensive care unit; **IG**: intervention group; **IQR**: interquartile range; **n.a.**: not available; **n.s.**: not (statistically) significant; **ICU**: Intensive Care Unit; **QoL**: Quality of life; **RCT**: randomized controlled trial

Table G: Ongoing trials of interest (11 July, 2016)

Author	Title*	Registration Number and status
Ahmedzai	A phase III randomised trial, with integral feasibility stage, to assess changes in quality of life and survival in patients being referred for early than versus standard specialist palliative care on being diagnosed with stage IV non-small cell lung cancer	ISRCTN13337289 Recruiting
Bakitas	Randomized Trial of ENABLE CHF-PC for Heart Failure Patients and Caregivers. (Comprehensive Heartcare For Patients and Caregivers)	NCT02505425 This study is enrolling participants by invitation only
Bénite	Impact on Quality of Life of an Early Management Supportive Care of Patients With Acute Leukemia in First Relapse	NCT02631811 This study is currently recruiting participants
Bernard	A Randomized Study of Early Palliative Care Integrated With Standard Oncology Care Versus Oncology Care Alone in Patients With Non-colorectal Gastrointestinal Malignancies	NCT02311465 This study has been withdrawn prior to enrollment
Chauhan	A multicentre non-blinded randomised controlled trial to assess the impact of regular early specialist symptom control treatment on quality of life in malignant mesothelioma (RESPECT-MESO): study protocol for a randomised controlled trial	ISRCTN18955704 Recruiting
Denvir	Randomised Trial of Early Versus Delayed Future Care Planning for Patients and Families Living With Advanced Heart Disease	NCT02302014 This study has been completed
Evans	Optimising palliative care for older people in community settings: development and evaluation of a new short term integrated service (phases 1b and 2)	ISRCTN45837097 Completed, no longer recruiting
Eychmüller	A Structured Early Palliative Care Intervention for Patients With Advanced Cancer - a Randomized Controlled Trial With a Nested Qualitative Study (SENS Trial)	NCT01983956 This study is currently recruiting participants
Ferrell	Integration of Palliative Care for Cancer Patients on Phase I Trials	1R01CA177562-01A1 Project End Date: 08/31/2019
Finley	Evaluation of the Implementation of an Early Integrated Palliative Care Program in the Esophageal Cancer Population	NCT02547142
Groenvold	Danish Palliative Care Trial (DanPaCT): A Randomised Clinical Multi-centre Trial Investigating the Effect of Specialised Palliative Care on Symptoms, Survival, Economical Factors and Satisfaction in Patients With Cancer Reporting Palliative Needs	NCT01348048 This study has been completed
Groote	Comparative Effectiveness Research in long term care facilities in Europe - randomised controlled cluster trial on 'PACE Steps to Success' palliative care programme	ISRCTN14741671 No longer recruiting
Hawley	Early Integrated Supportive Care Study for Gastrointestinal Cancer Patients.	NCT02335619 This study is currently recruiting participants
Janssens	Can Early Introduction of Specialized Palliative Care Limit Intensive Care, Emergency and Hospital Admissions in Patients With Severe and Very Severe COPD? A Randomized Study	NCT02223780 This study is currently recruiting participants
Kirven	An Examination of Palliative Care as Standard Practice for Heart Failure Patients	NCT01519479 This study has been completed
Lee	Pilot Study on H.O.P.E: Helping Ovarian Cancer Patients Cope During Disease Recurrence	NCT02090582 This study is ongoing, but not recruiting participants
Lin	Early Palliative Care With Standard Oncology Care Versus Standard Oncology Care Alone in Metastatic Esophageal Squamous Carcinoma (ESCC) and Gastric Cancer	NCT02375997 This study is currently recruiting participants
McDonnell Holstad	The Living Well Project: Early Palliative Care and Motivational Interviewing (MI) for Persons With AIDS	NCT01848483 This study is currently recruiting participants
Olesen	A Shared Care Approach for Seriously Ill Cancer Patients Between	NCT00594971

	General Practice, Discharge Department and a Specialist Palliative Care Team	This study has been withdrawn prior to enrollment.
Paiva	A Phase II Randomized Controlled Trial to Evaluate a Brief Psychosocial Intervention Together With Early Palliative Care in Reducing Depressive Symptoms of Patients With Advanced Cancer Starting First Line Palliative Chemotherapy	NCT02133274 This study is currently recruiting participants
Pantilat	A Randomized Controlled Trial for Patients With Heart Failure	NCT01461681 This study has been completed
Rodríguez	Management of Symptoms in Patients With Advanced Lung Cancer: Early Incorporation of Patient and Family to Attention and Care Program in Oncology	NCT01631565 This study is currently recruiting participants
Slomka	Randomized Trial of an HIV Navigation Program for Early Palliative Care	NCT01884389 This study is ongoing, but not recruiting participants
Sun	Integration of Palliative Care Planning in Pancreatic and Ovarian Cancers	NCT01927393 This study has been withdrawn prior to enrollment
Temel	Randomized Study of a Targeted Inpatient Supportive Care Intervention in Patients Hospitalized for Hematopoietic Stem Cell Transplantation (HSCT)	NCT02207322 This study is ongoing, but not recruiting participants
Temel	Randomized Study of Early Palliative Care Integrated With Standard Oncology Care Versus Standard Oncology Care Alone in Patients With Incurable Lung or Non-Colorectal Gastrointestinal Malignancies	NCT02349412 This study is currently recruiting participants
Tonkin	Evaluation of the clinical and cost effectiveness of Short-term Integrated Palliative Care Services (SIPC) to OPTimise CARE for people with advanced long-term Neurological conditions (OPTCARE Neuro)	ISRCTN18337380 Recruiting
Touzet	Impact of Early Palliative Care on Quality of Life and Survival of Patients With Non-small-cell Metastatic Lung Cancer in Northern France	NCT02308865 This study is currently recruiting participants
Treasure	A Pilot Study of Structured Palliative Care for Patients Enrolled on Phase I Clinical Trials	NCT02543541 This study is currently recruiting participants
Vanbelle	Effect of Early Palliative Care on Quality of Life of Patients With Advanced Cancer: a Randomised Controlled Trial	NCT01865396 This study is ongoing, but not recruiting participants
Woo	Randomized Controlled Trials for the Effect of Early Management on PAin and DEpression in Patients With PancreatoBiliary Cancer, EPADE-PB	NCT01589328 This study is currently recruiting participants
Wray	Early Symptom Control and Palliative Care Referral for Advanced Hepatocellular Carcinoma; a Randomized Control Trial	NCT02556619 This study is not yet open for participant recruitment

*The “official title” (clinicaltrials.gov) and the “scientific title” (isrctn.com) are shown here

Table H: Differences between protocol and publication

Protocol versus publication	Justification
-hospice care instead of hospice in Medline -MeSH "palliative medicine" included as MeSH and as free text in Medline, since it was introduced in 2015 -Five "intervention" terms included as extra cluster to enhance specificity: "team, intervention, service, visit, consultation" in Medline -sensitivity- and precision-maximizing was applied, not the sensitivity-maximizing version	The search strategy was modified in order to balance sensitivity and precision
SPC intervention: studies with a minority (<25%) of patients treated at home were also included in the review in the publication	This enabled the inclusion of Jordhøy et al.
Subgroup analysis: Elderly vs younger: not <79 but <60; 60-70; >70 years	This classification made more sense after evaluating the age of patients of RCTs
Subgroup analysis: hospitals vs hospices vs community settings: not available	All studies took place in hospitals
Adverse events could not be evaluated	Different from drug RCTs, adverse events were not reported in SPC RCTs
Protocol: "We will include all measures for QoL that include items from at least two of the four domains (physical, psychological, social, or spiritual) in our meta-analysis."	This would mean that ESAS should be included in the QoL analysis but this was not the case, since ESAS focuses on symptoms.
The CHEERS checklist was not used in the publication. Evaluation of the quality of the RCTs was considered as sufficient.	CHEERS was not appropriate or necessary, since none of the retrieved studies was primarily a cost-analysis.

CHEERS: Consolidated Health Economic Evaluation Reporting Standards; **ESAS**: Edmonton Symptom Assessment System; **QoL**: quality of life; **RCT**: randomized controlled trial; **SPC**: specialist palliative care

Fig A Secondary outcomes: completion rate of the primary outcome

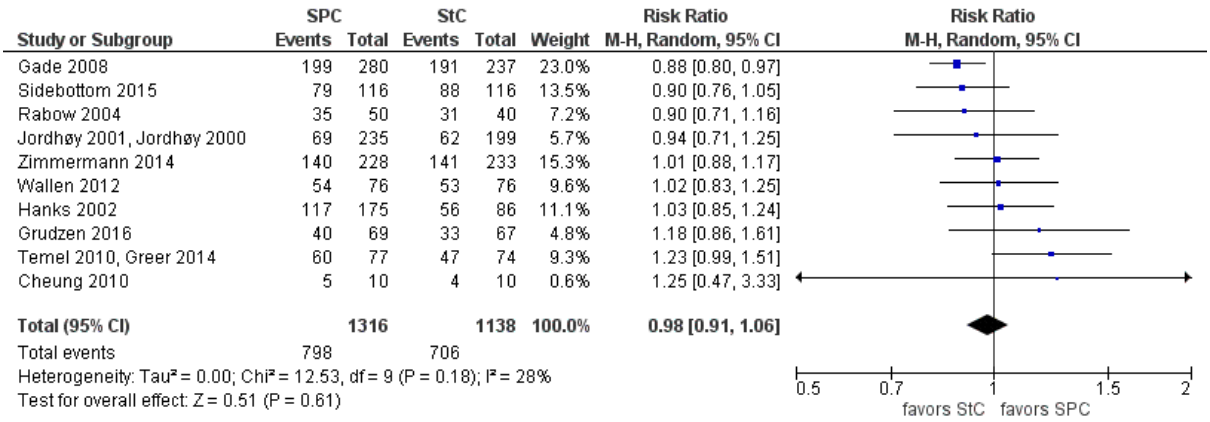

Fig B Primary outcome: quality of life; sensitivity analysis: Subgroup analysis: early versus not early (Sidebottom included)

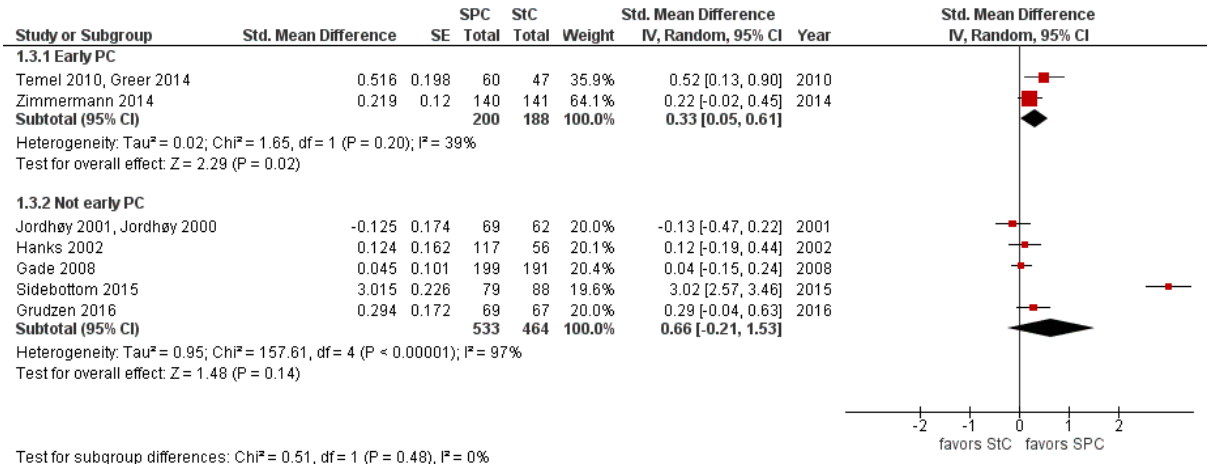

Fig C Primary outcome: quality of life; sensitivity analysis: Subgroup analysis: age (Sidebottom excluded)

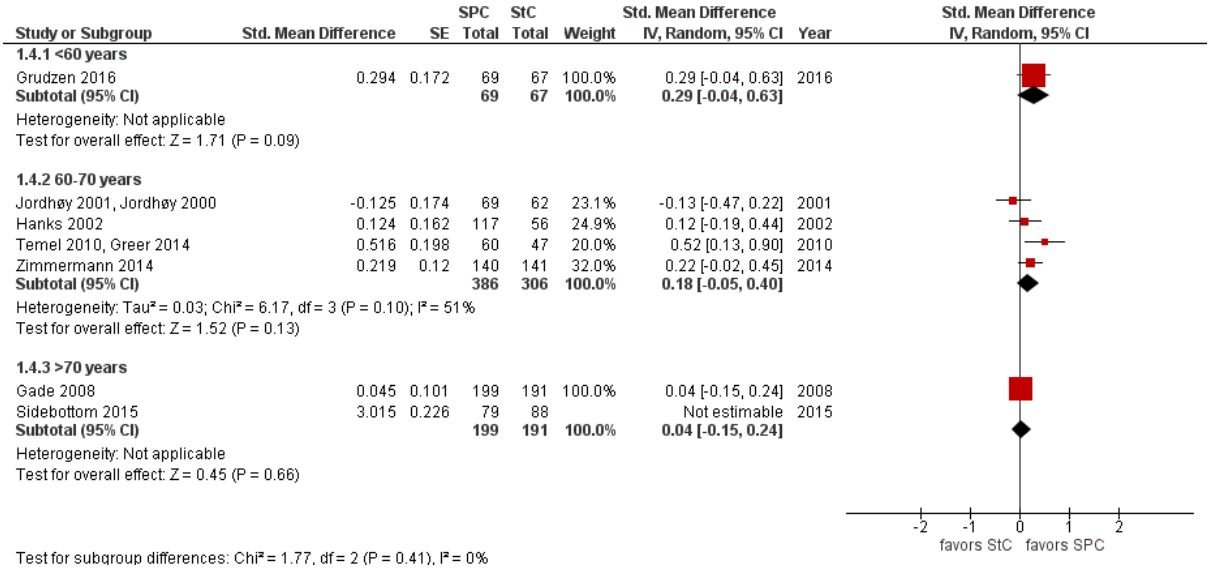

Fig D Secondary outcome: subgroup analysis: ESAS (sum score, range: 0-90)

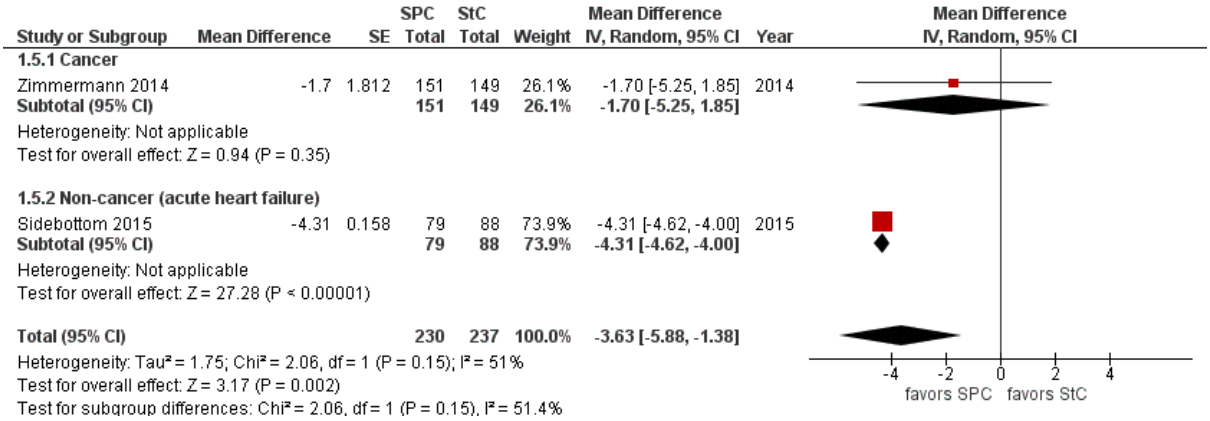

Fig E Secondary outcomes: subgroup analysis: depression

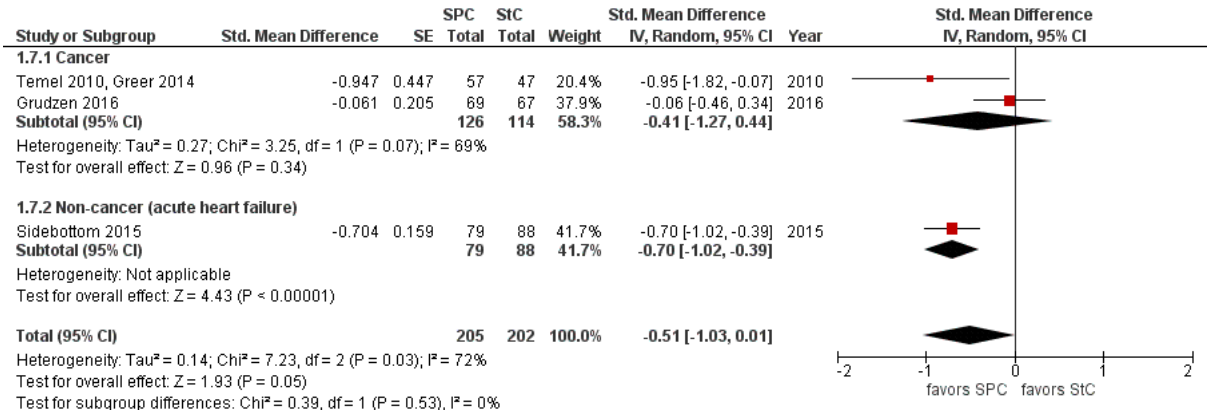

Fig F Secondary outcomes: subgroup analysis: Depression; early versus not early (equates outpatients versus inpatients)

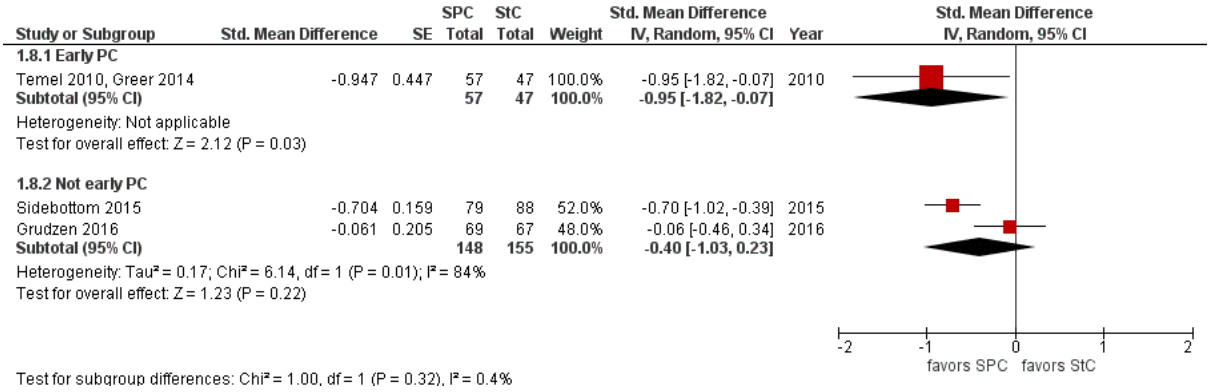

Fig G Secondary outcomes: subgroup analysis: depressions: age

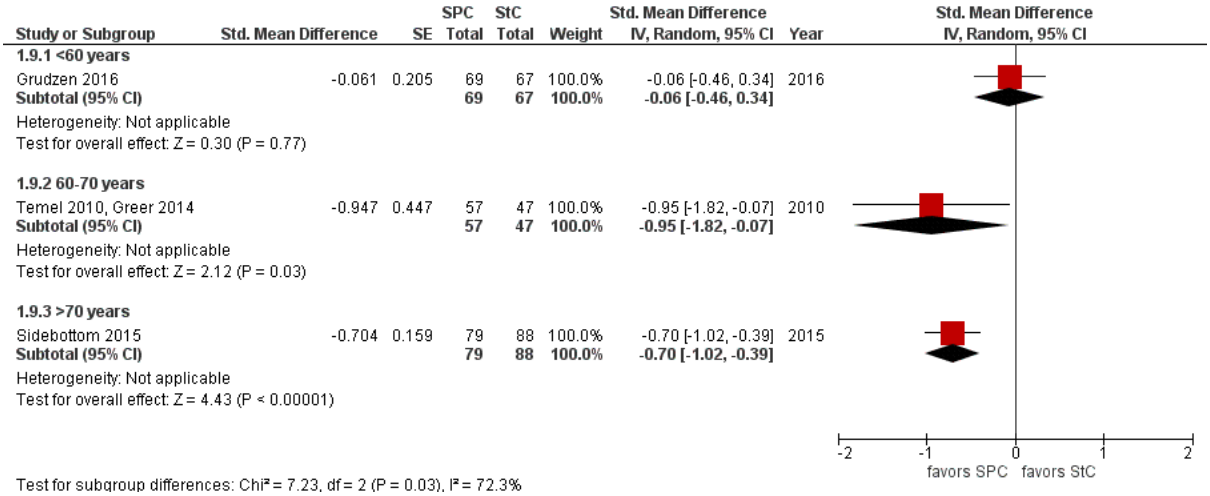

Fig H Secondary outcomes: subgroup analysis: survival [Hazard ratio; StC as reference]

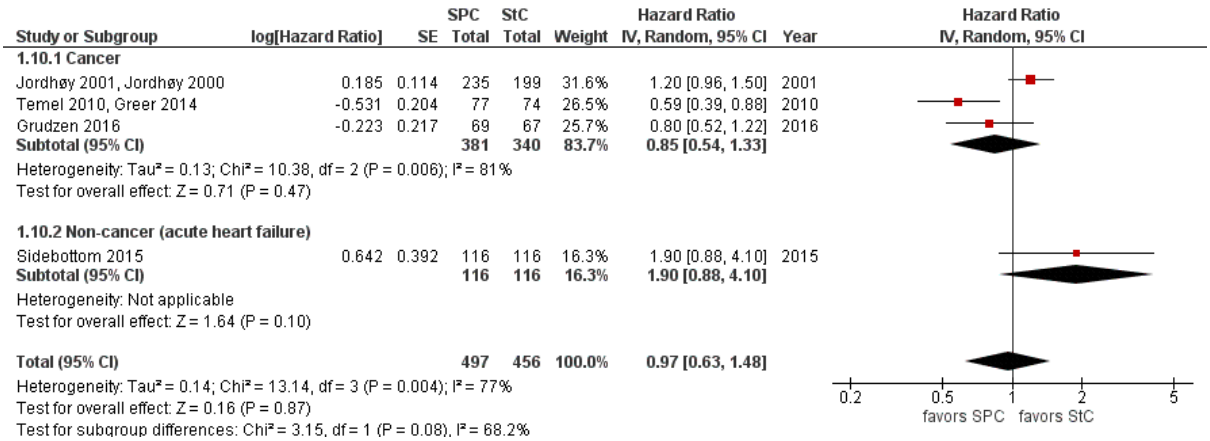

Fig I Secondary outcomes: subgroup analysis: Survival; early versus not early [Hazard ratio] (equates the comparison outpatients versus inpatients)

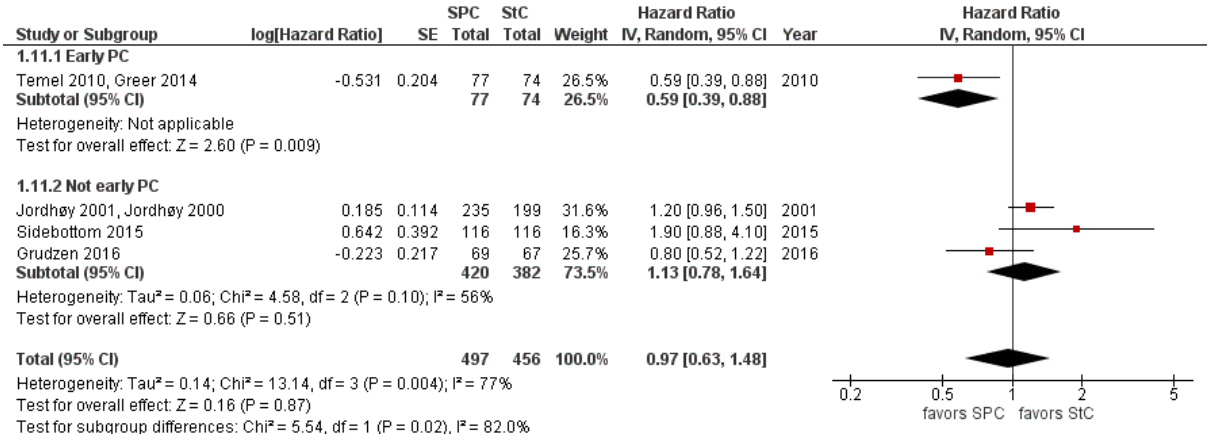

Fig J Secondary outcomes: subgroup analysis: age [Hazard ratio]